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(54) Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and methods for preparing them

Kristalle von N-(Trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanin und Verfahren zu ihrer Herstellung

Cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine et procédés pour leur préparation

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(73) Proprietor: **Ajinomoto Co., Inc.**
Tokyo 104 (JP)

(72) Inventors:
- **Sumikawa, Michito,**
  Central Research Lab.
  Kawasaki-shi, Kanagawa-ken (JP)
- **Koguchi, Yoshihito,**
  Central Research Lab.
  Kawasaki-shi, Kanagawa-ken (JP)
- **Ohgane, Takao,**
  Central Research Lab.
  Kawasaki-shi, Kanagawa-ken (JP)
- **Irie, Yasuo,**
  Central Research Lab.
  Kawasaki-shi, Kanagawa-ken (JP)
- **Takahashi, Satoji,**
  Tokai Plant,
  Ajinomoto Co., Inc
  Yottukaichi-shi, Mie-ken (JP)

(74) Representative: **Nicholls, Kathryn Margaret et al**
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

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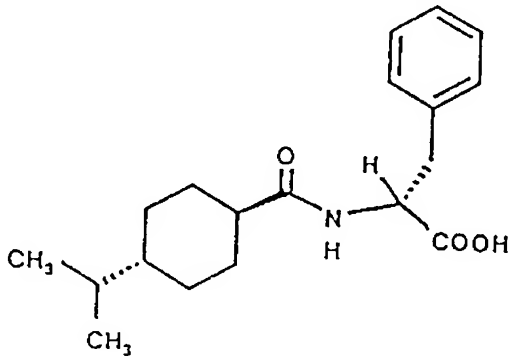
Description

The present invention relates to a crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and to methods for the production of that crystalline form.

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine of formula (1) is a known substance having therapeutic utility in depressing blood glucose levels.



(1)

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is disclosed in Japanese Patent Application Laid Open No. 63-54321 (equivalent to EP-A-196222 and US-4816484) and in J. Med Chem 32, 1436. The Japanese application describes how the compound may be crystallised from aqueous methanol to yield crystals having a melting point of 129 to 130°C. These crystals are in a crystalline form referred to herein as "B-type". The X-ray powder diffraction pattern and infra-red spectrum of B type crystals are shown in Figs 1 and 2 respectively.

The known B-type crystals suffer from problems of instability, especially when subjected to mechanical grinding. The instability results, for example, in conversion of the B-type crystals into other forms. The instability of the B-type crystals means that they are not ideal for use in medicine. It is in general desirable that a medicinal product containing a crystalline active ingredient have a composition which is well defined and stable in terms of the crystalline form of the active ingredient. Conversion of one crystalline form into unknown amounts of different, or amorphous, forms during processing or storage is undesirable and in many cases would be regarded as analogous to the appearance of unquantified amounts of impurities in the product.

The present inventors have discovered a method for producing a crystalline form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine having improved stability over the known B-type. For instance, the crystals according to one aspect of the present invention have enhanced stability to grinding. Such crystals are therefore more suitable for use in medicines than those of the B-type. The crystals having enhanced stability have been designated "H-type" by the inventors.

According to a first aspect of the invention there is provided a method for the production of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine comprising treating N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine with a solvent at a temperature of at least 10°C and forming said crystals in said solvent at a temperature of at least 10°C.

In one embodiment of this method N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is dissolved in the solvent at a temperature of at least 10°C to form a solution and crystals are then crystallised from the solution at a temperature of at least 10°C.

Alternatively, N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is combined at a temperature of at least 10°C with a solvent in which it is incompletely soluble at that temperature, to form a suspension of solid N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, and said suspension is maintained at a temperature of at least 10°C.

According to a second aspect of the invention there are provided crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine as obtainable by the method of the first aspect.

According to a still further aspect crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine are provided which have at least one, and preferably all, of the following properties:

(a) a melting point in the range of 136 to 142°C;

(b) an X-ray diffraction pattern having maxima at approximately 2θ=8.1, 13.1, 19.6 and 19.9°; and

(c) an infra red spectrum having absorptions at about 1714, 1649, 1542 and 1214cm^{-1}. Such crystals are designated "H-type" herein.

Crystals of the second aspect of the invention desirably comprise enhanced amounts of H-type crystals relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

In the accompanying figures:

Fig 1 shows a powder X-ray diffraction pattern of B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine;

Fig 2 shows an infra red absorption spectrum of B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine;

Fig 3 shows a powder X-ray diffraction pattern of H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine;

Fig 4 shows an infra red absorption spectrum of H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Fig 5 shows differential scanning calorimeter (DSC) traces of: B-type crystals before grinding (Fig 5a); H-type crystals before grinding (Fig 5b); B-type crystals after grinding.

As was indicated above one aspect of the present invention provides N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in H-type crystalline form. Examples of the physical properties of the H-type crystals are as follows.

The inventors have measured the melting point of H-type crystals and found it to be in the range of 136° to 142°. By contrast, when the melting point of B-type crystals was measured by the same technique a melting point of 128° to 131°C was found.

Examples of powder X-ray diffraction patterns of H-type and B-type crystals may be found at Figs 3 and 1 respectively. The diffraction pattern of the H-type crystals shows maxima at 2θ values of 8.1, 13.1, 19.6 and 19.9° where 2θ is the angle between the primary beam projection and the diffracted beam. There are no reflections at these 2θ values in the diffraction pattern of the B-type crystals. The diffraction pattern of H-type crystals also displays strong reflections at 2θ values between about 15 and 17° while the B-type crystals give only weak reflections in this range of 2θ. H-type crystals of the present invention preferably display a powder X-ray diffraction pattern substantially the same as that shown in Fig 3.

Table 1 below sets out the principal reflections in the powder pattern of H-type crystals in terms of 2θ values and intensity. The data were obtained using a Philips PW1700 powder diffractometer and a scan speed of 0.05°/sec.

Table 1

degree	intensity	degree	intensity	degree	intensity
5.5	S	5.7	M	8.1	S
8.5	W	9.0	W	10.4	W
11.1	M	11.5	S	12.0	W
13.1	S	14.3	W	15.2	S
15.4	M	15.9	S	16.2	S
17.0	W	17.3	W	18.2	W
18.6	W	18.9	W	19.6	S
19.9	S	21.1	W	21.5	W
22.1	W	23.1	W	23.7	W
24.5	W	29.9	W		
S; strong, M; medium, W; weak					

An example of an infra red adsorption spectrum of H-type crystals, obtained by the KBr method is shown at Fig 4, and that of B-type crystals as obtained by the same method is shown at Fig 2. The infra red spectrum of the H-type crystals is characterised by absorptions at around 1714cm^{-1} 1649cm^{-1}, 1542cm^{-1} and 1214cm^{-1}, which absorptions are not present in the spectrum of the B-type crystals. H-type crystals of the present invention preferably display an infra red spectrum substantially the same as that shown in Fig 4.

The inventors carried out elementary analysis of both H-type and B type crystals and the results are shown in Table 2. These confirm that the two crystal types have the same chemical composition ($C_{19}H_{27}NO_3$)

Table 2

	C	H	N
Calculated data (H- or B-type)(%)	71.89	8.57	4.41
Measured data (H-type)(%)	71.98	8.69	4.33
Measured data (B-type)(%)	71.82	8.66	4.27

H-type crystals are preferably substantially stable to grinding. Stability to grinding may be assessed by measurement of an appropriate physical property before and after grinding. Where the physical property remains substantially unchanged substantial stability to grinding is indicated. Suitable physical properties for measurement include melting point, differential scanning calorimeter trace X-ray diffraction pattern and infra red absorption spectrum, particularly the X-ray diffraction pattern.

As mentioned above the first aspect of the invention provides a method for the production of crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine the method comprising treating N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine with a solvent at a temperature of at least 10°C and forming crystals in the solvent at a temperature of at least 10°C.

In one embodiment -4-isopropylcyclohexylcarbonyl)-D-phenylalanine is dissolved in the solvent at a temperature of at least 10°C. The solution may be produced by dissolving in a solvent any one or more of amorphous N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, B-type crystals of the compound, and solvates of the compound such as hydrates, methanolates, ethanolates, isopropanolates and acetonitrilates.

Crystals may then be formed by crystallisation from solution, the crystallisation from solution taking place at a temperature between 10°C and the boiling point of the solvent. The crystals thus formed generally comprise enhanced amounts of H-type crystals relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine. Preferably, the product is predominantly H-type crystals.

The dissolution and crystallisation at a temperature of at least 10°C may be carried out in several ways as will be apparent to those of skill in the art. For instance, N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine may be dissolved in a solvent, or mixture of solvents in which it is readily soluble at elevated temperatures but in which it is only sparingly soluble at lower temperatures (which are still at least 10°C). Dissolution at elevated temperature is, in this case, followed by cooling during which the desired H-type crystals crystallise out of solution. Solvents which are suitable for use in this way include esters, such as methyl acetate and ethyl acetate, toluene and acetonitrile. Mixed solvents comprising a good solvent in which N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is readily soluble, preferably, in amounts of at least 1 weight % at 30°C, and a poor solvent in which it is more sparingly soluble, preferably, in amounts of not more than 0.01% at 30°C, may also be employed provided that crystallisation from the mixture at a temperature of at least 10°C is possible using the selected solvent mixture.

An alternative way of achieving crystallisation from solution at a temperature of 10°C is to utilise the difference in solubility of the crystals in different solvents. For example, N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine may be dissolved in a good solvent in which it is highly soluble such as one in which it is soluble in amounts of at least 1 weight % at 30°C and the solution subsequently mixed with a poor solvent in which it is more sparingly soluble, such as one in which it is soluble in amounts of not more than 0.01% at 30°C. Thus, the solution of N-(trans -4-isopropylcyclohexylcarbonyl)-D-phenylalanine in the good solvent might be added to the poor solvent, while maintaining a temperature in excess of 10°C, or the poor solvent might be added to the solution of N-(trans-4 -isopropylcyclohexylcarbonyl)-D-phenylalanine in the good solvent, again while maintaining a temperature in excess of 10°C. Examples of good solvents include lower alcohols, such as methanol, ethanol and isopropanol, as well as acetone, tetrahydrofuran and dioxane. Examples of poor solvents are water, hexane and diethyl ether.

Whichever of the two alternative crystallisation methods is employed it is important that the crystallisation temperature be at least 10°C up to the boiling point of the solvent. If the temperature employed is lower than 10°C it is not possible to obtain good yields of H-type crystals. Preferably, crystallisation is effected at a temperature in the range of 10° to 60°C, especially preferably from 20° to 60°C.

Crystals which have come out of solution are preferably separated from the solvent e.g. by filtration or centrifuging and are desirably then dried for example at a temperature in the range of from 20°C to 100°C.

In an alternative embodiment of the first aspect of the invention solid N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is suspended at a temperature of at least 10°C in a solvent in which it is incompletely soluble, preferably only sparingly soluble, at that temperature. A suspension results in which particles of solid are dispersed, and remain incompletely dissolved in the solvent. Preferably the solids are maintained in a state of suspension by agitation e.g. by shaking or stirring. The suspension is kept at a temperature of 10°C or higher thereby to effect a transformation of the starting solids into product crystals.

The solid N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine suspended in suitable solvent may be of any type, such as amorphous, or in the form of B-type crystals and may be a solvate, e.g. hydrate, methanolate, ethanolate, isopropanolate or acetonitrilate. The amorphous powder may be derived by drying a solvate. Preferably, the suspension is maintained at a temperature of at least 10°C for sufficiently long that the product crystals contain enhanced amounts of H-type crystals relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Solvents suitable for use in this embodiment of the invention include water, esters such as methyl acetate and ethyl acetate, as well as toluene. Good solvents in which N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is more readily soluble for example in amounts of at least 1% by weight at 30°C, such as lower alcohols e.g. methanol, ethanol and isopropanol, as well as acetone, acetonitrile, tetrahydrofuran and dioxane may also be used provided they are used in combination with a solvent in which N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is only poorly soluble for example in amounts of 0.01 weight % or less, e.g. water, hexane or diethyl ether. Where a mixed solvent is employed the concentration of good solvent is generally 70% by volume or less. Where it exceeds 70% by volume the solubility of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in the mixed solvent would be so high that the yield of desired H-type crystals would be disadvantageously low. Generally, the use of a mixed solvent gives rise to a favourable result. Preferably, the amount of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine dispersed in the solvent is from 0.5% to 30% by weight of the resulting suspension. If it is more than 30% by weight then the slurry properties of the suspension are poor and it will be difficult to agitate. On the other hand, it is not efficient in terms of the volume of solvent required to use less than 0.5% by weight. Preferably the suspension includes from 1% to 15% by weight.

The suspension is maintained at a temperature from 10°C to the boiling point of the solvent, in general from 20°C to 70°C. Temperatures below 10°C do not facilitate transformation of the solids to H-type crystals. The time for which the suspension is left before H-type crystals may be collected from it varies depending on the nature of the solvent(s) used, the temperature and other factors, such as the quantity of solids in suspension and the size of the solid particles.

Generally, however, it may be in the range of from 10 minutes to 48 hours. By adding H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine to the dispersion as seed crystals, the time required to form H-type crystals may be shortened. The end point in formation of H-type crystals can be determined by sampling crystals from the suspension, for example by filtration during the course of the conversion followed by measuring the powder X-ray diffraction pattern or infra red absorption spectrum of the crystals.

The H-type crystals as obtained in the manner mentioned above can be separated from suspension by filtration or centrifugation. In isolating them, cooling may be effected, if desired. In that case, the cooling temperature is preferably no lower than 10°C. The isolated crystals are dried, for example at a temperature in the range of from 20 to 120°C.

According to another aspect of the invention there is provided a pharmaceutical composition comprising crystals as obtainable by the method of the first aspect, in particular H-type crystals, and a pharmaceutically acceptable excipient, diluent or carrier.

According to a still further aspect of the invention there is provided a method of manufacture of a pharmaceutical composition comprising mixing an effective amount of crystals as obtainable by the method of the first aspect of the invention, in particular H-type crystals and a pharmaceutically acceptable excipient diluent or carrier.

The crystals as obtainable by the method of the first aspect, particularly H-type crystals may be employed in a method for treatment of a human or other mammal to depress its blood glucose level comprising administering an effective amount of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine crystals.

Examples

Embodiments of the invention are illustrated below by way of example only.

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for use in the following examples was obtained by the method described in Example 3 of Japanese patent application laid open no. 63-54321. The product contained crystals of B-type.

(A) H-Type Crystals by Crystallisation from Solution Example A1

20ml of an acetone solution of 5g of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine were added dropwise to a stirred mixture of acetone (40ml) and water (60ml) at 25°C. After cooling to 10°C, the precipitated crystals were filtered and dried at 90°C at reduced pressure overnight. 4.5g of dry crystals were obtained. The crystals had a melting point of 138 to 141°C. The powder X-ray diffraction pattern and the infra-red absorption spectrum were measured and the crystals were thus identified as H-type.

Example A2

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (4g) was dissolved in a mixture of ethanol (50ml) and water (50ml) at 45°C. The solution was cooled with stirring. H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-

D-phenylalanine (0.1g) prepared in Example A1 were added at a temperature of 37°C and the solution was cooled further to 25°C. The crystals were filtered and dried at 60°C overnight and at reduced pressure. 2.5g of dry crystals were obtained. The crystals had a melting point of 138 to 141°C. The powder X-ray diffraction pattern and the infra-red absorption spectrum enabled the crystals to be identified as H-type.

Example A3

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (0.5g) was dissolved in acetonitrile at 45°C and the solution was cooled to 25°C. The precipitated crystals were filtered and dried at 90°C under reduced pressure. 0.48g of dry crystals were obtained. The crystals had a melting point of 138 to 141°C. Their powder X-ray diffraction pattern and infra red absorption spectrum were consistent with their being H-type crystals.

Comparative Example A1

The procedure of Example A1 was followed but cooling to 5°C was employed. 4.6g of dry crystals were obtained. The crystals had a melting point of 128 to 131°C. The powder X-ray diffraction pattern and the infra-red absorption spectrum of the crystals were measured and the crystals were identified as B-type.

Comparative Example A2

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (5g) was dissolved in a mixture of ethanol (60ml) and water (40ml) at 30°C. The solution was cooled to 5°C with stirring. The precipitated crystals were filtered and dried at 90°C under reduced pressure, and overnight. 3.3g of dried crystals were obtained. The crystals had a melting point of 128 to 131°C and their powder X-ray diffraction pattern and infra-red absorption spectrum indicated that they were of the B-type.

Comparative Example A3

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (5g) was dissolved in a mixture of methanol (70ml) and water (30ml) at 40°C. The solution was cooled to 5°C with stirring. The precipitated crystals were filtered and dried at 90°C under reduced pressure overnight. 3.5g of dry crystals were obtained. Once again, the crystals had a melting point of 128 to 131°C. The powder X-ray diffraction pattern and the infra-red absorption spectrum were consistent with the crystals being B-type.

(B) H-Type Crystals from Suspension

Example B1

B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (3g) were dispersed in 300ml of water and stirred at 30°C for 1 day. The crystals were filtered and dried at 90°C under reduced pressure overnight. 2.9g of dry crystals were obtained. The powder X-ray diffraction pattern and the infra-red absorption spectrum were recorded and indicated that the crystals were of H-type.

Example B2

B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (4g) were dispersed in a mixture of acetone (40ml) and water (60ml) and stirred at 20°C overnight. The crystals were subsequently filtered off and dried at 90°C under reduced pressure overnight. 3.6g of dry crystals were obtained. Powder X-ray diffraction and infra red absorption spectroscopy indicated that the product crystals were of H-type.

Example B3

Hydrate of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for use in this example was prepared as follows. 20g of B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine were dissolved in a mixture of ethanol (300ml) and water (200ml) at 30°C. The solution was cooled to 5°C with stirring. The precipitated crystals were filtered off and dried at 40°C under reduced pressure for 2 hours. 13.9g of dried crystals resulted.

4.2g of the hydrate was dispersed in a mixture of ethanol (30ml) and water (70ml) and stirred at 45°C overnight. The crystals were filtered off and dried at 90°C under reduced pressure overnight. 3.8g of dried crystals were obtained. These were found to be of the H-type by powder X-ray diffraction and infra red spectroscopy.

Example B4

4.2g of the hydrate of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine prepared as in example B3 was dispersed in a mixture of ethanol (30ml) and water (70ml). 40mg of H-type crystals were added and the dispersion was stirred at 45°C for 1 hour. The crystals were filtered off and dried at 90°C under reduced pressure overnight. 3.9g of dry crystals were obtained. These were found to be of the H-type by X-ray diffraction and infra red absorption spectroscopy.

Example B5

B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (5g) were dispersed in a mixture of isopropanol (25ml) and water (75ml) and stirred at 50°C for 10 hours. The resulting crystals were filtered off and dried at 90°C under reduced pressure overnight. 4.4g of dry crystals were obtained. These were found to be of the H-type by X-ray diffraction and infra red spectroscopy.

Comparative Example B1

4g of B-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine were dispersed in a mixture of acetone (40ml) and water (60ml) and stirred at 5°C overnight. The crystals were filtered off and dried at 90°C under reduced pressure overnight. 3.6g of dry crystals were obtained. The powder X-ray diffraction pattern and the infra red absorption spectrum were measured and the crystals were found to be of B-type.

(C) Stability to Grinding

In order to demonstrate the stability of H-type crystals to grinding the following experiment was carried out.

H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and the previously known B-type crystals were each mechanically ground in a grinder, and the X-ray diffraction pattern of each powder was measured and compared with the spectrum before grinding. No change was observed in the H-type crystals before and after grinding but changes were observed in the diffraction pattern of the B-type crystals.

Similarly, the differential scanning calorimeter (DSC) trace for each of the H-type, and B-type crystals was measured before and after grinding. Fig 5a shows the DSC trace of B-type crystals before grinding. The crystals show a sharp melting point at around 130°C. The DSC trace of H-type crystals before grinding is shown in Fig 5b. These crystals also demonstrated a sharp melting point at around 140°C. The DSC trace of the H-type crystals was unchanged by grinding. By contrast, the trace shown in Fig 5c for B-type crystals after grinding differs from the trace obtained before grinding and new troughs are visible in the trace.

Claims

Claims for the following Contracting States : AT, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A method for the production of crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine comprising treating N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine with a solvent at a temperature of at least 10°C and forming said crystals in said solvent at a temperature of at least 10°C.

2. A method according to claim 1 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is dissolved in the solvent at a temperature of at least 10°C to form a solution and crystals are then crystallised from the solution at a temperature of at least 10°C.

3. A method according to claim 2 wherein crystallisation from solution is effected by reducing the temperature of the solution to a temperature of at least 10°C.

4. A method according to claim 2 wherein the crystallisation from solution is effected at a temperature of at least 10°C by adding to the solution a further solvent selected such that the solubility of said N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in the mixture of the solvent and further solvent is less than in the solvent, the solubility being reduced to an extent such that crystals form in the mixed solvent at a temperature in excess of 10°C.

5. A method according to claim 1 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is combined at a temperature of at least 10°C with a solvent in which it is incompletely soluble at that temperature to form a suspension of solid N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, and said suspension is maintained at a temperature of at least 10°C, thereby to form said crystals from said solids.

6. A method according to any one of the preceding claims further comprising separating said crystals from the solvent at a temperature in excess of 10°C.

7. Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine as obtainable by the method of any one of the preceding claims.

8. Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine having at least one of the following properties:

(a) a melting point in the range of 136-142°C;
(b) a powder X-ray diffraction pattern with reflection maxima at 2θ of about 8.1°, 13.1°, 19.6° and 19.9°;
(c) an infra red absorption spectrum with absorption bands in the region of 1714, 1649, 1542 and 1214cm^{-1}.

9. Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine according to claim 8 having all three of the properties (a), (b) and (c).

10. Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine having an X-ray powder diffraction pattern substantially as shown in Fig 3 and/or an infra red spectrum substantially as shown in Fig 4.

11. A pharmaceutical composition comprising crystals according to any one of claims 7 to 10 and a pharmaceutically acceptable excipient, diluent or carrier.

12. Crystals according to any one of claims 7 to 10 for pharmaceutical use.

13. Use of the crystals of any one of claims 7 to 10 in the manufacture of a medicament for reducing blood glucose levels in a mammal.

14. Crystals according to any one of claims 7 to 10 in the substantial absence of solvent.

Claims for the following Contracting State : ES

1. A method for the production of crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine comprising treating N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine with a solvent at a temperature of at least 10°C and forming said crystals in said solvent at a temperature of at least 10°C.

2. A method according to claim 1 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is dissolved in the solvent at a temperature of at least 10°C to form a solution and crystals are then crystallised from the solution at a temperature of at least 10°C.

3. A method according to claim 2 wherein crystallisation from solution is effected by reducing the temperature of the solution to a temperature of at least 10°C.

4. A method according to claim 2 wherein the crystallisation from solution is effected at a temperature of at least 10°C by adding to the solution a further solvent selected such that the solubility of said N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine in the mixture of the solvent and further solvent is less than in the solvent, the solubility being reduced to an extent such that crystals form in the mixed solvent at a temperature in excess of 10°C.

5. A method according to claim 1 wherein N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine is combined at a temperature of at least 10°C with a solvent in which it is incompletely soluble at that temperature to form a suspension of solid N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, and said suspension is maintained at a temperature of at least 10°C, thereby to form said crystals from said solids.

6. A method according to any one of the preceding claims further comprising separating said crystals from the solvent at a temperature in excess of 10°C.

7. A method according to any one of claims 1 to 6 wherein product crystals contain an enhanced proportion, relative to the starting N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, of crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine having at least one of the following properties:

(a) a melting point in the range of 136-142°C;
(b) a powder X-ray diffraction pattern with reflection maxima at 2θ of about 8.1°, 13.1°, 19.6° and 19.9°;
(c) an infra red absorption spectrum with absorption bands in the region of 1714, 1649, 1542 and 1214cm^{-1}.

8. A method according to claim 7 wherein product crystals have an enhanced proportion of crystals having all three of the properties (a), (b) and (c).

9. A method according to any one of the preceding claims wherein the product crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine have an X-ray powder diffraction pattern substantially as shown in Fig 3 and/or an infra red spectrum substantially as shown in Fig 4.

10. A method for the production of a pharmaceutical composition comprising admixing crystals as produced by the method of any one of claims 1 to 9 and a pharmaceutically acceptable excipient, diluent or carrier.

11. Use of crystals as obtainable by the method of any one of Claims 1 to 9 in the manufacture of a medicament for the reduction of blood glucose in a mammal.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verfahren zur Herstellung von Kristallen von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin, welches das Behandeln von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin mit einem Lösungsmittel bei einer Temperatur von mindestens 10°C und Ausbilden der Kristalle in dem Lösungsmittel bei einer Temperatur von mindestens 10°C umfaßt.

2. Verfahren nach Anspruch 1, bei dem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin in dem Lösungsmittel bei einer Temperatur von mindestens 10°C unter Bildung einer Lösung gelöst wird und danach Kristalle aus der Lösung bei einer Temperatur von mindestens 10°C auskristallisiert werden.

3. Verfahren nach Anspruch 2, bei dem die Kristallisation aus der Lösung durch Erniedrigen der Temperatur der Lösung auf eine Temperatur von mindestens 10°C durchgeführt wird.

4. Verfahren nach Anspruch 2, bei dem die Kristallisation aus der Lösung bei einer Temperatur von mindestens 10°C durchgeführt wird, indem der Lösung ein weiteres Lösungsmittel zugesetzt wird, das so ausgewählt ist, daß die Löslichkeit des N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanins in dem Gemisch aus dem Lösungsmittel und dem weiteren Lösungsmittel geringer ist als in dem Lösungsmittel, wobei die Löslichkeit soweit vermindert wird, daß in dem Mischlösungsmittel sich Kristalle bei einer Temperatur von mehr als 10°C bilden.

5. Verfahren nach Anspruch 1, bei dem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin bei einer Temperatur von mindestens 10°C mit einem Lösungsmittel kombiniert wird, in welchem es bei dieser Temperatur unvollständig löslich ist, so daß eine Suspension von festem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin gebildet wird und die Suspension bei einer Temperatur von mindestens 10°C gehalten wird, wobei Kristalle aus dem Feststoff gebildet werden.

6. Verfahren nach einem der vorhergehenden Patentansprüche, welches weiterhin das Abtrennen der Kristalle aus dem Lösungsmittel bei einer Temperatur von mehr als 10°C umfaßt.

7. Kristalle von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin, erhältlich durch das Verfahren nach einem der vorhergehenden Patentansprüche.

8. Kristalle von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin, die mindestens eine der nachfolgenden Eigenschaften aufweisen:

(a) einen Schmelzpunkt im Bereich von 136 bis 142°C,
(b) ein Pulver-Röntgenbeugungsmuster mit Reflexionsmaxima bei 2θ von etwa 8,1°, 13,1°, 19,6° und 19,9°,
(c) ein Infrarotabsorptionsspektrum mit Absorptionsbanden im Bereich von 1714, 1649, 1542 und 1214 cm^{-1}.

9. Kristalle von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin gemäß Anspruch 8, die alle der drei Eigen-

schaften (a), (b) und (c) aufweisen.

10. Kristalle von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin mit einem Pulver-Röntgenbeugungsspektrum im wesentlichen wie in Fig. 3 gezeigt und/oder einem Infrarotspektrum im wesentlichen wie in Fig. 4 gezeigt.

11. Arzneimittelzusammensetzung, enthaltend Kristalle nach einem der Ansprüche 7 bis 10 und ein pharmazeutisch geeignetes Streckmittel, Verdünnungsmittel oder Trägermaterial.

12. Kristalle nach einem der Ansprüche 7 bis 10 zur pharmazeutischen Verwendung.

13. Verwendung der Kristalle nach einem der Ansprüche 7 bis 10 zur Herstellung eines Arzneimittels zur Senkung des Blutglucosespiegels in einem Säuger.

14. Kristalle nach einem der Ansprüche 7 bis 10 in der praktischen Abwesenheit von Lösungsmitteln.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von Kristallen von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin, welches das Behandeln von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin mit einem Lösungsmittel bei einer Temperatur von mindestens 10°C und Ausbilden der Kristalle in dem Lösungsmittel bei einer Temperatur von mindestens 10°C umfaßt.

2. Verfahren nach Anspruch 1, bei dem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin in dem Lösungsmittel bei einer Temperatur von mindestens 10°C unter Bildung einer Lösung gelöst wird und danach Kristalle aus der Lösung bei einer Temperatur von mindestens 10°C auskristallisiert werden.

3. Verfahren nach Anspruch 2, bei dem die Kristallisation aus der Lösung durch Erniedrigen der Temperatur der Lösung auf eine Temperatur von mindestens 10°C durchgeführt wird.

4. Verfahren nach Anspruch 2, bei dem die Kristallisation aus der Lösung bei einer Temperatur von mindestens 10°C durchgeführt wird, indem der Lösung ein weiteres Lösungsmittel zugesetzt wird, das so ausgewählt ist, daß die Löslichkeit des N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanins in dem Gemisch aus dem Lösungsmittel und dem weiteren Lösungsmittel geringer ist als in dem Lösungsmittel, wobei die Löslichkeit soweit vermindert wird, daß in dem Mischlösungsmittel sich Kristalle bei einer Temperatur von mehr als 10°C bilden.

5. Verfahren nach Anspruch 1, bei dem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin bei einer Temperatur von mindestens 10°C mit einem Lösungsmittel kombiniert wird, in welchem es bei dieser Temperatur unvollständig löslich ist, so daß eine Suspension von festem N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin gebildet wird und die Suspension bei einer Temperatur von mindestens 10°C gehalten wird, wobei Kristalle aus dem Feststoff gebildet werden.

6. Verfahren nach einem der vorhergehenden Patentansprüche, welches weiterhin das Abtrennen der Kristalle aus dem Lösungsmittel bei einer Temperatur von mehr als 10°C umfaßt.

7. Verfahren nach einem der Ansprüche 1 bis 6, wobei die als Produkt gebildeten Kristalle einen gegenüber dem als Ausgangsmaterial eingesetzten N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin erhöhten Anteil an Kristallen von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin enthalten, die mindestens eine der nachfolgenden Eigenschaften aufweisen:

   (a) einen Schmelzpunkt im Bereich von 136 bis 142°C,
   (b) ein Pulver-Röntgenbeugungsmuster mit Reflexionsmaxima bei 2θ von etwa 8,1°, 13,1°, 19,6° und 19,9°,
   (c) ein Infrarotabsorptionsspektrum mit Absorptionsbanden im Bereich von 1714, 1649, 1542 und 1214 cm^{-1}.

8. Verfahren nach Anspruch 7, wobei die als Produkt gebildeten Kristalle einen erhöhten Anteil von Kristallen enthalten, die alle der drei Eigenschaften (a), (b) und (c) aufweisen.

9. Verfahren nach einem der vorhergehenden Patentansprüche, wobei die als Produkt gebildeten Kristalle von N-(trans-4-Isopropylcyclohexylcarbonyl)-D-phenylalanin ein Pulver-Röntgenbeugungsmuster im wesentlichen wie in Figur 3 gezeigt und/oder ein Infrarotabsorptionsspektrum im wesentlichen wie in Figur 4 gezeigt aufweisen.

10. Verfahren zur Herstellung einer Arzneimittelzusammensetzung, welches das Vermischen von Kristallen, hergestellt mit Hilfe des Verfahrens nach einem der Ansprüche 1 bis 9, mit einem pharmazeutisch geeigneten Streckmittel, Verdünnungsmittel oder Trägermaterial umfaßt.

11. Verwendung von Kristallen, die durch das Verfahren nach einem der Ansprüche 1 bis 9 erhältlich sind, zur Herstellung eines Arzneimittels zum Erniedrigen des Blutglukosespiegels in einem Säuger.

Revendications

Revendications pour les Etats contractants suivants : AT, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Procédé de production de cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine comprenant le traitement de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine avec un solvant à une température d'au moins 10°C et la formation desdits cristaux dans ledit solvant à une température d'au moins 10°C.

2. Procédé selon la revendication 1, dans lequel on dissout la N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine dans le solvant à une température d'au moins 10°C pour former une solution, puis on fait cristalliser les cristaux dans la solution à une température d'au moins 10°C.

3. Procédé selon la revendication 2, dans lequel on effectue la cristallisation dans la solution en abaissant la température de la solution à une température d'au moins 10°C.

4. Procédé selon la revendication 2, dans lequel on effectue la cristallisation dans la solution à une température d'au moins 10°C en ajoutant à la solution un autre solvant choisi de façon que la solubilité de ladite N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine dans le mélange du solvant et de l'autre solvant soit plus basse que dans le solvant, la solubilité étant réduite dans une mesure telle que des cristaux se forment dans le solvant mixte à une température supérieure à 10°C.

5. Procédé selon la revendication 1, dans lequel on combine la N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine, à une température d'au moins 10°C, avec un solvant dans lequel elle n'est pas complètement soluble à cette température pour former une suspension de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine solide, et on maintient ladite suspension à une température d'au moins 10°C, pour former ainsi lesdits cristaux à partir dudit solide.

6. Procédé selon l'une quelconque des revendications précédentes, qui comprend en outre la séparation desdits cristaux à partir du solvant à une température supérieure à 10°C.

7. Cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine, tels qu'ils peuvent être obtenus par le procédé selon l'une quelconque des revendications précédentes.

8. Cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine ayant au moins l'une des propriétés suivantes:

   (a) un point de fusion compris entre 136 et 142°C;
   (b) un diagramme de diffraction des rayons X de la poudre ayant des maximums de réflexion à 2θ d'environ 8,1°; 13,1°; 19,6° et 19,9°.
   (c) un spectre d'absorption infrarouge ayant des bandes d'absorption dans la région de 1714, 1649, 1542 et 1214 cm^{-1}.

9. Cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine selon la revendication 8, ayant les trois propriétés (a), (b) et (c).

10. Cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine, ayant un diagramme de diffraction des rayons X de la poudre essentiellement similaire à celui présenté dans la figure 3 et/ou un spectre infrarouge essentiellement similaire à celui présenté dans la figure 4.

11. Composition pharmaceutique contenant des cristaux selon l'une quelconque des revendications 7 à 10 et un excipient, diluant ou support pharmaceutiquement acceptable.

12. Cristaux selon l'une quelconque des revendications 7 à 10, à utiliser en pharmacie.

13. Utilisation des cristaux selon l'une quelconque des revendications 7 à 10 dans la fabrication d'un médicament destiné à la réduction des taux de glucose sanguin chez un mammifère.

14. Cristaux selon l'une quelconque des revendications 7 à 10, essentiellement sans solvant.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de production de cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine comprenant le traitement de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine avec un solvant à une température d'au moins 10°C et la formation desdits cristaux dans ledit solvant à une température d'au moins 10°C.

2. Procédé selon la revendication 1, dans lequel on dissout la N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine dans le solvant à une température d'au moins 10°C pour former une solution, puis on fait cristalliser les cristaux dans la solution à une température d'au moins 10°C.

3. Procédé selon la revendication 2, dans lequel on effectue la cristallisation dans la solution en abaissant la température de la solution à une température d'au moins 10°C.

4. Procédé selon la revendication 2, dans lequel on effectue la cristallisation dans la solution à une température d'au moins 10°C en ajoutant à la solution un autre solvant choisi de façon que la solubilité de ladite N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine dans le mélange du solvant et de l'autre solvant soit plus basse que dans le solvant, la solubilité étant réduite dans une mesure telle que des cristaux se forment dans le solvant mixte à une température supérieure à 10°C.

5. Procédé selon la revendication 1, dans lequel on combine la N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine, à une température d'au moins 10°C, avec un solvant dans lequel elle n'est pas complètement soluble à cette température pour former une suspension de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine solide, et on maintient ladite suspension à une température d'au moins 10°C, pour former ainsi lesdits cristaux à partir dudit solide.

6. Procédé selon l'une quelconque des revendications précédentes, qui comprend en outre la séparation desdits cristaux à partir du solvant à une température supérieure à 10°C.

7. Procédé selon l'une quelconque des revendications précédentes, dans lequel les cristaux produits contiennent une proportion accrue, par rapport à la N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine de départ, de cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine ayant au moins l'une des propriétés suivantes:

   (a) un point de fusion compris entre 136 et 142°C;
   (b) un diagramme de diffraction des rayons X de la poudre ayant des maximums de réflexion à 2θ d'environ 8,1°; 13,1°; 19,6° et 19,9°.
   (c) un spectre d'absorption infrarouge ayant des bandes d'absorption dans la région de 1714, 1649, 1542 et 1214 cm^{-1}.

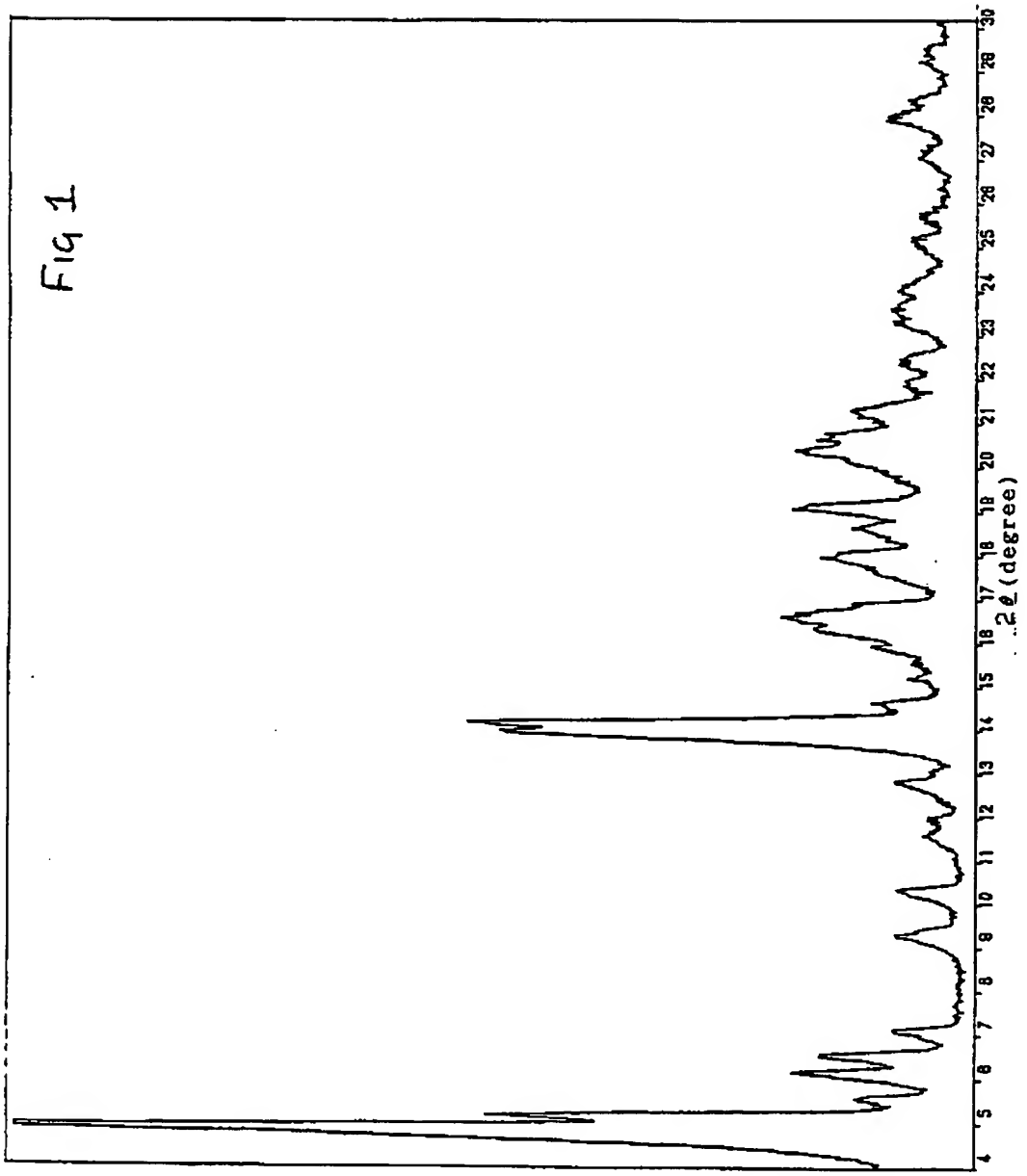
8. Procédé selon la revendication 7, dans lequel les cristaux produits ont une proportion accrue de cristaux ayant les trois propriétés (a), (b) et (c).

9. Procédé selon l'une quelconque des revendications précédentes, dans lequel les cristaux de N-(trans-4-isopropylcyclohexylcarbonyl)-D-phénylalanine produits ont un diagramme de diffraction des rayons X de la poudre essentiellement similaire à celui présenté dans la figure 3 et/ou un spectre infrarouge essentiellement similaire à celui présenté dans la figure 4.

10. Procédé de production d'une composition pharmaceutique comprenant le mélange de cristaux tels que produits par le procédé selon l'une quelconque des revendications 1 à 9 avec un excipient, un diluant ou un support pharmaceutiquement acceptable.

11. Utilisation de cristaux tels qu'ils peuvent être obtenus selon l'une quelconque des revendications 1 à 9 dans la fabrication d'un médicament destiné à la réduction des taux de glucose sanguin chez un mammifère.

Fig 1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2θ(degree)

Fig 2

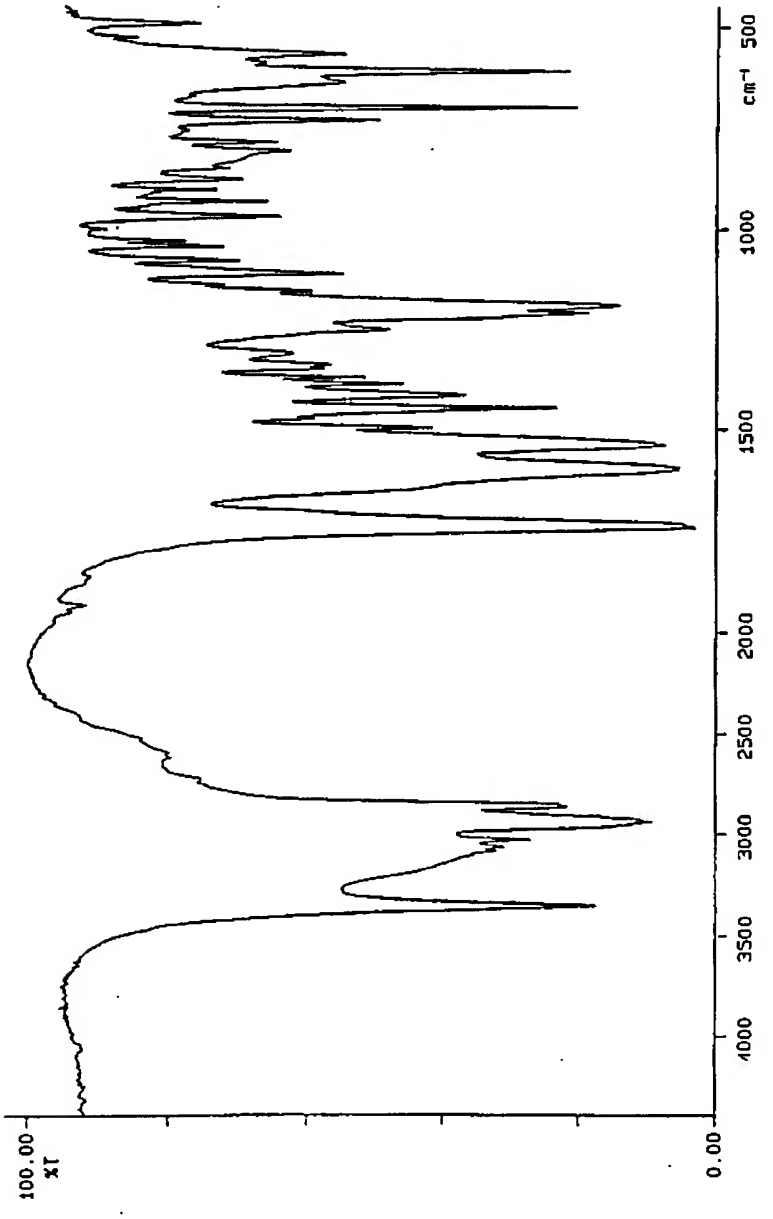

Fig 3

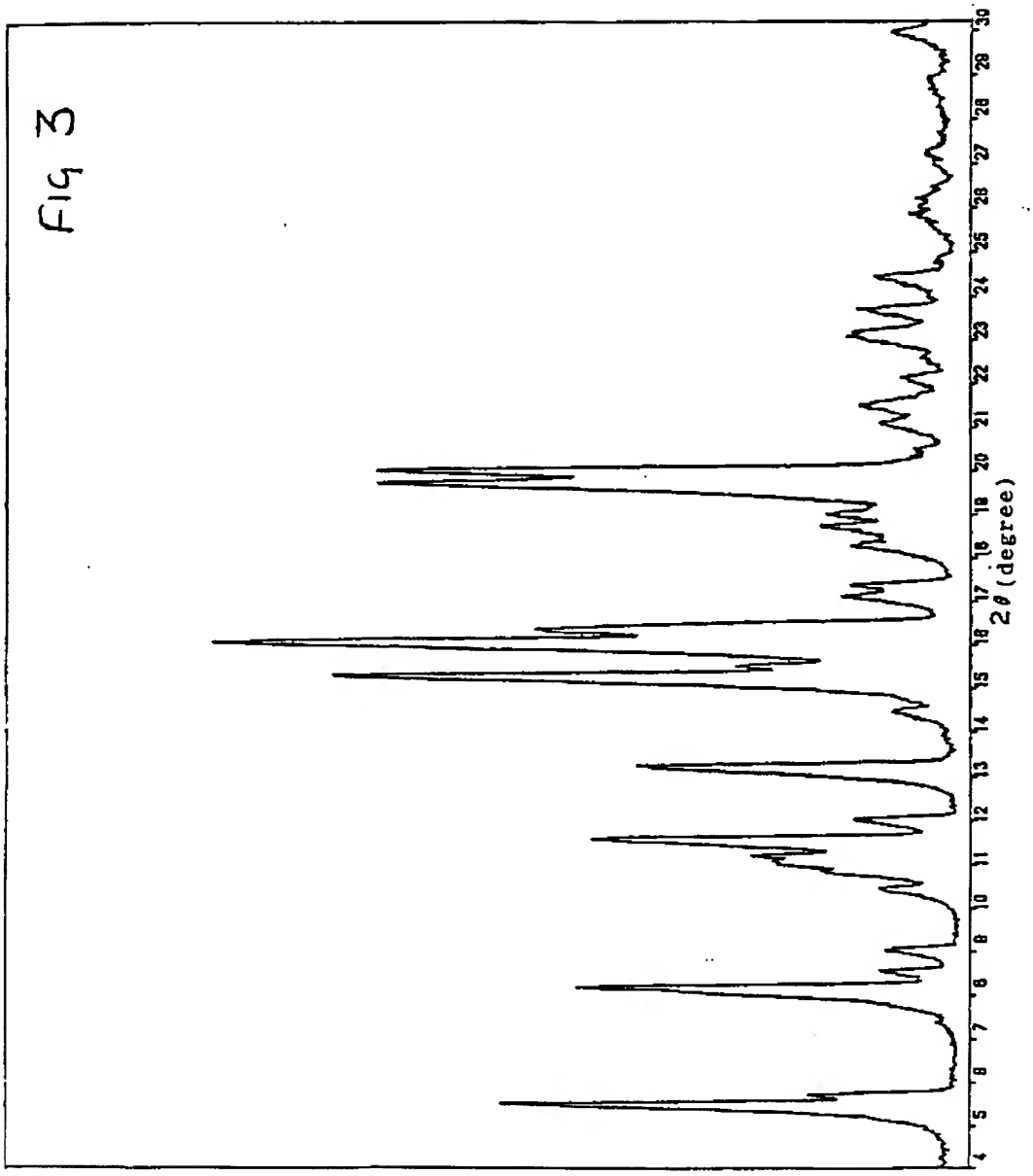

Fig 4

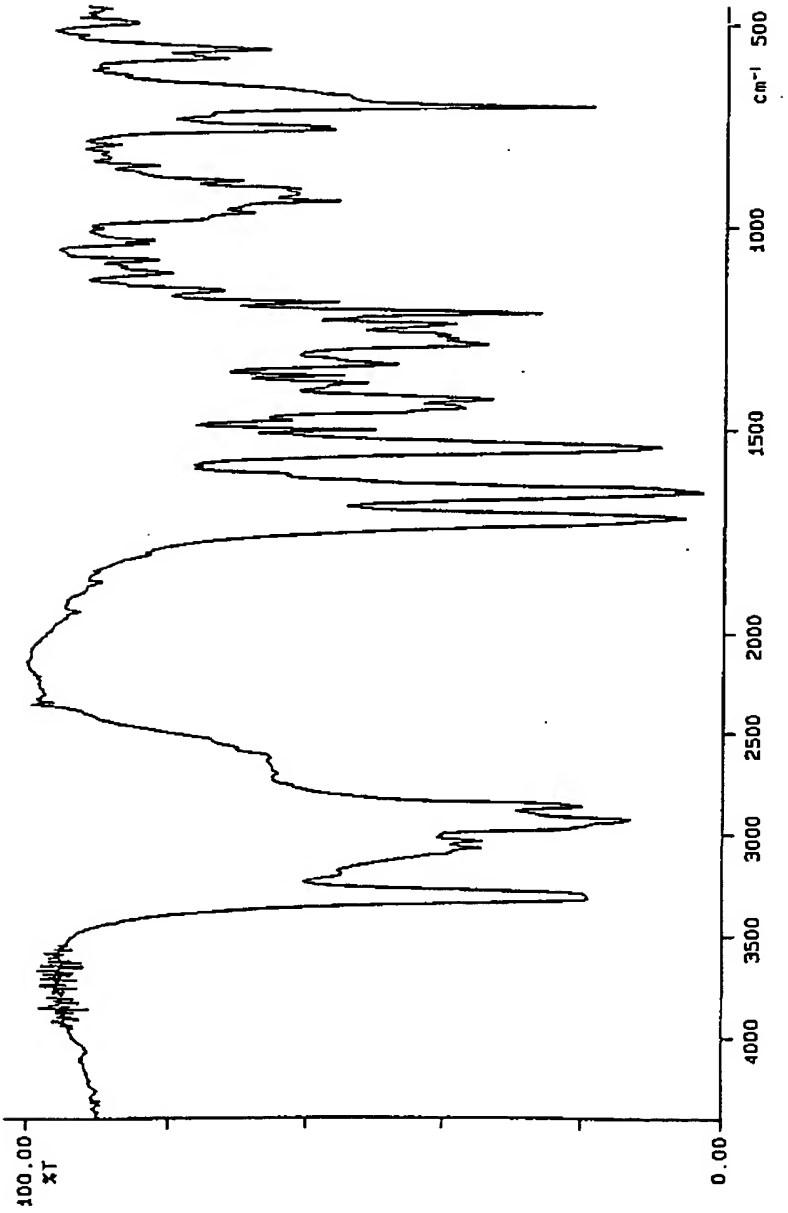

FIG 5a

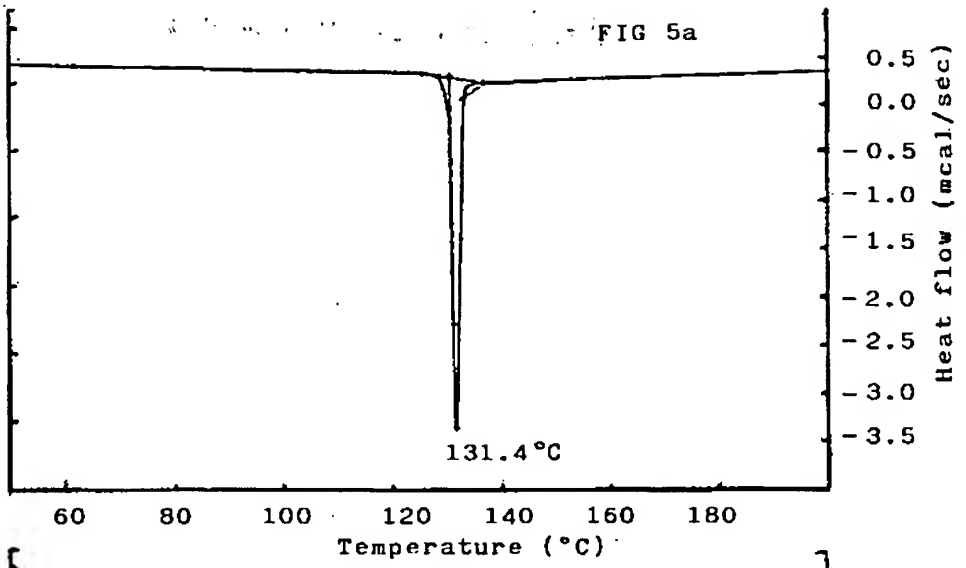

FIG 5b

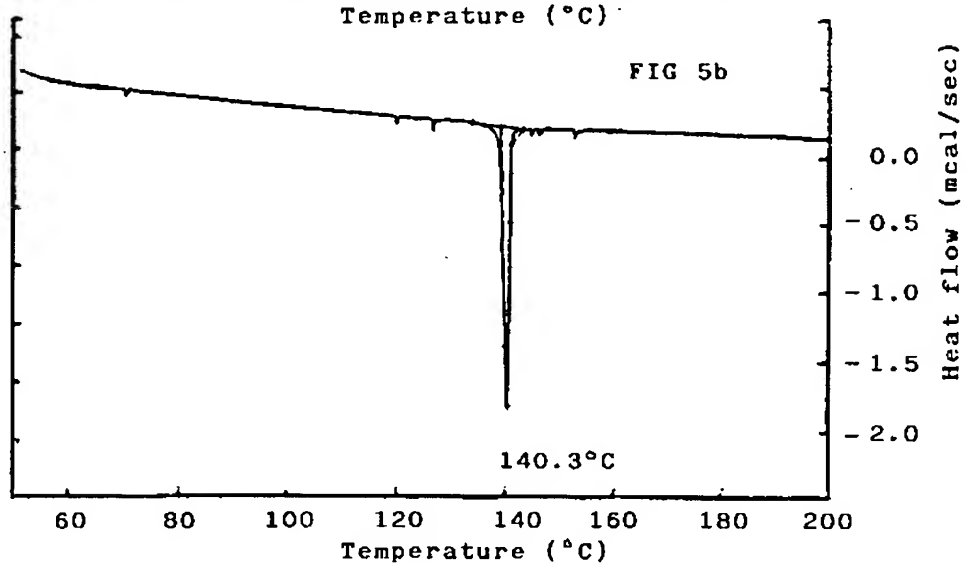

FIG 5c